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MINIREVIEWS

Histone deacetylases and cardiovascular cell lineage commitment

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Abstract

Cardiovascular diseases (CVDs), which include all diseases of the heart and circulation system, are the leading cause of deaths on the globally. During the development of CVDs, choric inflammatory, lipid metabolism disorder and endothelial dysfunction are widely recognized risk factors. Recently, the new treatment for CVDs that designed to regenerate the damaged myocardium and injured vascular endothelium and improve recovery by the use of stem cells, attracts more and more public attention. Histone deacetylases (HDACs) are a family of enzymes that remove acetyl groups from lysine residues of histone proteins allowing the histones to wrap the DNA more tightly and commonly known as epigenetic regulators of gene transcription. HDACs play indispensable roles in nearly all biological processes, such as transcriptional regulation, cell cycle progression and developmental events, and have originally shown to be involved in cancer and neurological diseases. HDACs are also found to play crucial roles in cardiovascular diseases by modulating vascular cell homeostasis (*e.g.*, proliferation, migration, and apoptosis of both ECs and SMCs). This review focuses on the roles of different members of HDACs and HDAC inhibitor on stem cell/ progenitor cell differentiation toward vascular cell lineages (endothelial cells, smooth muscle cells and Cardiomyocytes) and its potential therapeutics.

Key words: Histone deacetylases; Stem cell; Endothelial cell; Smooth muscle cell; Cardiovascular diseases

Core tip: Stem cell differentiation toward vascular cell lineages is an area of important active research at present. Histone deacetylases (HDACs) are found to play important roles in cardiovascular diseases. Through modulating the homeostasis of acetylation status in histone and non-histone proteins and regulating grow factor activities, HDACs participate in stem cell differentiation and vascular cell homeostasis. In this review we provide an update on the roles of HDACs

and HDAC inhibitors on stem cell differentiation toward vascular cell lineages.

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INTRODUCTION

Cardiovascular diseases (CVDs) are the number one killer of human beings globally, which is a class of disorders of the heart and blood vessels. CVDs include all diseases of the heart and circulation system, including coronary heart disease, angina, heart attack, congenital heart disease and stroke. Coronary heart disease (angina and heart attack) and stroke may be caused by the same problem - atherosclerosis[1].

Atherosclerosis is a chronic inflammation process marked with thickened artery wall as a result of invasion and accumulation of fatty material (called atheroma) inside arteries. During this process, the endothelium, as the major regulator of vascular homeostasis, shows a number of vasoprotective effects, such as vasodilation, suppression of smooth muscle cell growth, and inhibition of inflammatory responses[2]. Accumulating evidence suggests that endothelial dysfunction is an early marker for atherosclerosis and can be detected and repaired prior to structural changes within the vessel wall[3].

Normally the repairing treatments for injured vascular endothelium include physical exercise and drug treatments aimed at reducing cardiovascular risk factors, such as lowering cholesterol, antihypertensive therapy, smoking cessation and some regulator replacement strategies such as angiotensin-converting enzyme 2 inhibitor therapy, estrogen replacement therapy in postmenopausal women, supplementation with folic acid[4]. Recently, a new therapeutic strategy, that designed to regenerate the damaged myocardium and injured vascular endothelium and improve recovery by the use of stem cells, attracts more and more public attention[5]. Till now, there has not established a specific cell type to serve best the treatment of CVDs. Many stem cell types such as embryonic stem cells (ESCs), adult stem cells and induced pluripotent stem cells have the ability to differentiate into vascular cell lineages *in vitro*.

Stem cell therapy is based on the stem cell characters, the potential to differentiate into specific cell types under different stimulation and proliferate to replace damaged cells with healthy functional ones[6]. Like any biological process, the differentiation of stem cell involves gene expression reprogramming *via* histone acetylation homeostasis mediated chromatin remodelling. Histone deacetylases (HDACs) are key components of the regulating system that controls histone acetylation homeostasis. HDACs play an essential role in multiple biology processes regulating cell survival, proliferation and apoptosis *via* histone and non-histone protein modification. Accumulating evidence showed that HDACs play an important role in vascular remodelling[7].

HDACS

Histone acetylation is a reversible process characterized by histone and non-histone protein acetyl-transferase transferring the acetyl moiety from acetyl co-enzyme A to lysine residues. HDACs are a family of enzymes that remove acetyl groups from the N-acetylated lysine residues on histones[8] and non-histone proteins. Histone acetylation/ deacetylation alters chromosome structure and affects transcription factors access to DNA[9]. Accumulating evidence indicates that HDACs play a fundamental role in transcriptional regulation, cell cycle progression, and contribute to developmental events.

Mammalian genome encodes 18 HDACs, which can be grouped into four classes based on the homology with yeast histone deacetylases[10]. All members share a highly conserved deacetylase domain but differ in structure, subcellular localization and expression pattern, which results in different cellular functions[11]. Class Ⅰ HDACs (homologous to yeast Rpd3) comprise of HDAC1, -2, -3 and -8, which are widely expressed in many human tissues and cell lines. Among them both HDAC3 and HDAC8 can shuttle between the cytosol and the nucleus, while HDAC1 and HDAC2 are exclusively located in nucleus[12,13]. The deacetylation of histones to repress gene transcription is the main function of class Ⅰ HDACs. Class Ⅰ HDACs form large multi-subunit complex that associates with transcription factors and other chromatin modifiers, except HDAC8 whose function is not clearly clarified[14]. In mammals, HDAC1 and -2 can bind to each other forming the catalytic core of three different complexes: Sin3, nucleosome remodelling deacetylase and corepressor of RE1-silencing transcription factor. HDAC3 can form two different multi-protein complexes, nuclear receptor corepressor and silencing mediator of retinoic acid and thyroid hormone receptors. Class Ⅰ HDACs are mainly found in such nuclear complexes. Furthermore, the association with several different proteins show an essential role in regulating their activity, which is highly pronounced in developmental processes that requires a global modulation of transcriptional programmes. With the exception of HDAC8, knockout of class Ⅰ HDACs in mice have indeed resulted in embryonic lethality[15].

Class Ⅱ HDACs can be divided into two sub-class groups. Class Ⅱa members include HDAC4, -5, -7, -9, while class Ⅱb comprises of HDAC6 and -10. Class Ⅱ HDACs differ from Class Ⅰ mainly for their tissue-

specific expression pattern and the considerable lower deacetylase activity. Besides, their length (almost the double of Class Ⅰ HDACs) and cellular localization are all different. Class Ⅱ HDACs can shuttle between nucleus and cytoplasm. Class Ⅱa HDACs have conserved binding sites for the transcription factor myocyte enhancer factor 2 and the chaperone protein 14-3-3, which help HDACs shuttle from the nucleus to the cytoplasm. The nuclear-cytoplasm shuttling and occurrence of post-translational modification such as phosphorylation, indicates their primary role as signal transducers in numerous tissues during development and disease[16].

Class Ⅱb family includes HDAC6 and HDAC10. HDAC10 presents a leucin-rich domain at the C-terminal. Recent reports showed HDAC10 might be upregulated on human myeloma cell lines[17]. HDAC6 is different from all other HDACs, as it harbours two deacetylase domains and a C-terminal zinc finger, being the important cytoplasmic deacetylase in mammalian cells[18]. Cytoskeletal proteins such as α-tubulin and cortactin, transmembrane proteins such as the interferon-α receptor, and chaperones are all targets of HDAC6[19,20].

Class Ⅲ HDACs comprises a group of protein called Sirtuins (SIRT1-7). Although they possess a deacetylase domain, they diverge from classical HDACs as their enzymatic activity requires the cofactor NAD+. This feature suggests their involvement in metabolic functions[21]. HDAC11 is the last discovered and the only member of Class Ⅳ HDACs[22]. This review will focus on the classical HDACs, class Ⅰ and Ⅱ HDACs. The protein length, cellular location and potential cellular functions of these HDACs can be referred to references[11,23].

HDACS AND ENDOTHELIAL CELL DIFFERENTIATION

In response to vascular injury, endothelial cell (EC) migration and proliferation contribute to the repairing of the damaged EC or denuded endothelium. Recent reports show that circulating or local resident stem/progenitor cell differentiation is also involved in this process[24]. Through modulating chromatin structures and non-histone transcription factors, HDACs are involved in the gene expression reprograming in multiple biological processes such as cell-cycle, cell differentiation and survival[25]. Therefore, the involvement of HDACs in EC differentiation is expected.

The first evidence came from studies with HDAC inhibitors (HDACi). HDACi decreases endothelial lineage commitment of endothelial progenitor cells[26,27]. Rössig *et al*[27] found that the suppressive effect of HDACi on EC differentiation was mediated by the down-regulation of homeobox transcription factor HoxA9, which directs the transcription of EC markers such as eNOS, VEGFR2 and VE-cadherin, suggesting that the HDAC-dependent activation of Hox-A9 is essential for EC differentiation[27].

There is no direct evidence that HDAC1, 2 and 8 are involved in EC differentiation, although indirect evidence indicates that HDAC1 may suppress EC differentiation. Rajasingh *et al*[28] showed that HDACs inhibitor, trichostatin A, improved AceH3K9 and reduced HDAC1 expression in bone marrow progenitor cells, leading to differentiation into myocytes and ECs, which suggests that HDAC1 plays a suppressive role in bone marrow progenitor cell differentiation toward EC lineage[28]. Different from other members within class Ⅰ HDACs, accumulating evidence suggests that HDAC3 possesses a pivotal function in stem cells differentiation into ECs, which is capable of repairing the damaged endothelium. VEGF is a well-known EC differentiation inducer. Xiao *et al*[29] reported that VEGF up-regulated HDAC3 in ESC-derived $Sca1^+$ cells. Over-expression of HDAC3 *via* adenoviral gene transfer increased, while trichostatin A or HDAC3 siRNA abolished VEGF-induced EC marker expression in $Sca1^+$ cells, suggesting HDAC3 may function downstream of VEGF signal pathway[29]. Our study[29] and reports from Illi B[30] demonstrated that laminar flow enhanced ESC-derived progenitor cell differentiation into EC lineage in an HDAC dependent manner. We found that laminar flow stabilized and activated HDAC3 through the Flk-1-PI3K-Akt pathway in a ligand independent manner, which in turn deacetylated p53, leading to p21 activation, contributing to EC differentiation[31]. Similar mechanism is involved in VEGF-induced EC differentiation, in which HDAC3 modulates differentiation process *via* regulating non-histone proteins. Our recent study found that unconventional splicing of HDAC3 might change HDAC3 function, inducing endothelial-to-mesenchymal transition[32]. These reports suggest a critical role of HDAC3 in EC fate determination.

Class Ⅱ HDACs seem not directly involved in EC differentiation. Several groups tried to link class Ⅱ HDACs with EC differentiation, but no solid evidence has been obtained. In Spallotta *et al*[33,34]'s reports, nitric oxide induced a cross-talk between class I HDACs (HDAC3) and class Ⅱ HDACs (HDAC4 and 7), which might contribute to the neovascularization in ischemic tissue and skin repairing[33,34]. However, the effect of nitric oxide on EC differentiation may be largely derived from HDACs-mediated global hypoacetylation on pluripotency maintaining genes like Oct4, Nanog, KLF4, *etc.* Considering class Ⅱ HDACs have only weak deacetylase activity, the histone hypoacetylation might be mainly caused by HDAC3 in the complex. Reports from other groups indicate that HDAC7 may participate in EC proliferation and cell-to-cell contact but is not involved in EC differentiation[35,36]. A recent report from Song *et al*[37] showed that AMPK activation participated in endothelial colony forming cells differentiation. During this process, HDAC5 could be phosphorylated by AMPK. However, there is no direct evidence on the involvement of HDAC5.

HDACS AND SMOOTH MUSCLE CELL DIFFERENTIATION

Smooth muscle cells (SMCs) are the major cellular components within vessel wall, located in the tunica media controlling the calibre of the vessel. It is widely believed that in response to vascular injury SMCs in the tunica media undergo from contractile to synthetic phenotype change, followed by the migration into the intima and proliferation, contributing to the neointima formation. However, recent reports show that stem/progenitor cell-derived SMCs play an important role in neointima formation and atherosclerosis, but the origin of the progenitor cells is controversial. Reports from Shimizu *et al*[38], Han *et al*[39] and Li *et al*[40] support the notion that the circulating bone-marrow-derived progenitor cells contribute to SMC differentiation and neointimation formation, but reports from Hu *et al*[41] and Tang *et al*[42] exclude the involvement of bone marrow-derived progenitor cells. They demonstrated that SMCs in the lesion area were mainly derived from local resident progenitor cells.

HDACs play diverse roles in SMC differentiation depending on the HDAC species, stem cell source and stimulus, exerting promoting or suppressive effects. Except HDAC1, all other three members of class Ⅰ HDACs are reported to be involved in SMC differentiation. In response to oxidized lipids or PDGF, HDAC2 forms a complex with Class Ⅱ HDACs (HDAC4/5) to deacetylate histone H4 in SMC marker gene promoter region, thereby suppressing SMC differentiation[43,44]. Recently, Liu *et al*[45] reported that HDAC2 exerted suppressive effect on bone marrow mesenchymal stem cells to SMCs differentiation[45]. In contrast, HDAC3 and 8 may play a positive role in SMC differentiation. Loss of HDAC3 in neural crest caused deficiency of aortic arch artery SMCs in midgestation during embryonic development *via* down-regulation of Notch signalling, suggesting a positive regulatory role of HDAC3 in the neural crest-derived smooth muscle lineage[46]. Several reports demonstrate that HDAC8 is critical for SMC differentiation, therefore HDAC8 is even regarded as a novel SMC differentiation marker[13,47,48]. The involvement of class Ⅱ HDACs in SMC differentiation seems restricted to HDAC4, 5 and 7. Different from the suppressive role of HDAC4 and 5 from the reports by Yoshida *et al*[43,44], studies from Glenisson *et al*[49] revealed that HDAC4 is necessary for SMC marker expression in TGFβ1-induced myofibroblast differentiation[49]. Our group found that different isoforms of HDAC7 might play opposite function in SMC differentiation. During ESC differentiation toward SMC lineage, HDAC7 mRNA underwent further splicing, which was enhanced by PDGF. The full spliced HDAC7 increased SMC marker expression through modulating the SRF-myocardin complex while the partially spliced HDAC7 decreased SMC marker expression by degrading myocyte enhancer factor 2C[50].

HDACS AND CARDIOMYOCYTES DIFFERENTIATION

Cardiomyocytes (CMs) build the atria and ventricles of the heart, which are critical to the proper form during the beating of the heart. So the differentiation towards CMs is a prerequisite and an essential part of heart development[51].

The effect of class Ⅰ HDACs on CM differentiation seems a bit controversial, especially on HDAC1. Opposite effect of HDAC1 on CM differentiation has been reported by different groups. Dovey *et al*[52] reported that HDAC1 deficiency in ESCs increases CM marker expression in the embryoid bodies, suggesting a suppressive role of HDAC1 in CM differentiation. Lu *et al*[53,54] also reported that HDAC1 exerted negative effect on cardiac cell differentiation from mesenchymal stem cells under a myocardial microenvironment. The suppressive role of HDAC1 was further supported by Liu *et al*[55] as down-regulation of HDAC1 promoted cardiac cell differentiation. However, Hoxha *et al*[56,57] reported that HDAC1 knockdown decreased CMs marker expression in ES and induced pluripotent stem cells, suggesting a supportive role in CMs differentiation. HDAC1 favours stem cell differentiation *via* turning off pluripotency genes by modulating histone acetylation and DNA methylation. HDAC2 may play a positive role in CM differentiation, contributing to angiotensin Ⅱ-induced cardiac hypertrophy[58]. In contrast, HDAC3 suppresses CM differentiation through modulating transcription factor Tbx5, preventing the pre-maturation of cardiac progenitor cells[59].

Current reports revealed that Class Ⅱ HDACs mainly played a suppressive role in CMs differentiation. The inhibition of HDAC4 facilitates c-kit(+) cardiac stem cells to differentiate into cardiac lineage, leading to cardiogenesis and the restoration of cardiac function in myocardial infarction mouse model[60]. Ha *et al*[61] reported that retention of HDAC5 in nucleus suppressed cardiac foetal gene expression and CMs hypertrophy. Gene disruption studies from Chang *et al*[62] revealed that HDAC5 or 9 deficiency induced cardiac hypertrophy in mice.

Depending on the stem cell source and stimulus, different HDACs may play different roles in stem cell differentiation toward different cell lineages. HDACs and their potential roles in cardiovascular lineage commitment are summarized in Table 1. Different HDACs (HDAC1, 2, 3, 4, 5, 7, 8) play different roles in stem cell differentiation toward different cell lineages, HDACs and their potential roles in cardiovascular lineage(ECs, SMCs, CSCs) commitment are summarized in Table 1.

HDACS INHIBITORS

The role of HDACs in injured vessel repairing and stem/progenitor cell differentiation derived originally from

Table 1 Summary of histone deacetylases' effect on endothelial cell, smooth muscle cell and cardiomyocyte differentiation

Commitment	HDACs	Characterization	Ref.
EC	HDAC1	EC differentiation markers ↓	[28]
	HDAC3	EC differentiation markers ↑	[29]
		In vitro and *in vivo* angiogenesis	[31]
		In vivo ability to repair injured vessels	
	HDAC4	EC differentiation	[33,34]
	HDAC5	Endothelial colony forming cells differentiation	[37]
	HDAC7	EC differentiation	[33-35]
		Maintenance of vascular integrity	
		Promote angiogenesis	
SMC	HDAC2	Involved in suppressing SMC differentiation	[43,44]
	HDAC3	Neural crest-derived smooth muscle cell differentiation ↓	[43]
	HDAC4	Involved in suppressing SMC differentiation	[44]
	HDAC5	Involved in suppressing SMC differentiation	[44]
	HADC7	Full spliced HDAC7 SMC differentiation markers ↑	[50]
	HADC7	Unspliced HDAC7 SMC differentiation markers ↓	[50]
	HDAC8	Marker of smooth muscle differentiation	[13]
CM	HDAC1	CM differentiation ↑	[56,57]
	HDAC1	CM differentiation ↓	[52-55]
	HDAC2	Induce CMs hypertrophy	[58]
	HDAC3	Regulate early cardiogenesis	[59]
	HDAC4	CSC-derived cardiac regeneration	[60]
		Restoration of cardiac function ↑	

EC: Endothelial cell; SMC: Smooth muscle cell; CM: Cardiomyocyte; CSC: Cardiac stem cell; HDAC: Histone deacetylase.

investigations on HDACi, which are a large number of natural and synthetic compounds. Generally, HDACi can be divided into 4 classes according to their chemical structure: hydroxamic acids, short chain fatty acids, cyclic tetra-peptides, and benzamides[63]. These HDACi share the presence of an active group targeting a three-part structure consisting of a zinc-binding group of HDACs and inhibits their enzymatic activity. Some HDACi are able to discriminate HDACs among different classes and a few of them can even inhibit a single member[64,65]. In addition to suppress the deacetylase activity of HDACs, HDACi may exert functions in HDAC-independent way, like through SP1[66]. HDACi has been shown to regulate multiple cellular processes, including cell apoptosis and survival, proliferation and growth arrest, senescence, differentiation, immunogenicity, *etc*. Some kinds of HDACi are used in clinical trials as therapeutic drug against cancers. Detailed information on this aspect won't be discussed in this review.

SUMMARY AND PERSPECTIVES

CVDs characterized by vascular injury are one of the greatest health challenges we have been facing for decades. During the development of CVDs, HDACs play a critical role in various signal pathways by modulating vascular cell homeostasis (*e.g.*, proliferation, migration, and apoptosis of both ECs and SMCs) and stem cell differentiation towards vascular cells. HDAC3 and HDAC7 have been proved to be capable of directing stem cell differentiation towards ECs and SMCs respectively. Through modulating the homeostasis of acetylation status in histone and non-histone proteins and regulating grow factor activities, HDACs participate in stem cell differentiation and vascular cell homeostasis. Targeting HDACs activities and their inhibitors' effect on injured vessel and heart will undoubtedly provide new therapeutic strategies for the treatment of CVDs.

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